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             20   144: Pascal_1973-2007/Apr W4
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      Examined 100 files
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              2   203: AGRIS_1974-2007/Feb
              1   315: ChemEng & Biotec Abs_1970-2007/Apr
      Examined 150 files
              6   340: CLAIMS(R)/US Patent_1950-07/May 03
              1   342: Derwent Patents Citation Indx_1978-07/200727
              1   345: Inpadoc/Fam.& Legal Stat_1968-2007/UD=200718
              9   348: EUROPEAN PATENTS_1978-2007/ 200716
             86   349: PCT FULLTEXT_1979-2007/UB=20070503UT=20070426
             16   357: Derwent Biotech Res.__1982-2007/May W1
              1   358: Current BioTech Abs_1983-2006/Jan
              2   388: PEDS: Defense Program Summaries_1999/May
             28   399: CA SEARCH(R)_1967-2007/UD=14620
              1   434: SciSearch(R) Cited Ref Sci_1974-1989/Dec
             48   440: Current Contents Search(R)_1990-2007/May 09
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*File 654: IPCR/8 classification codes now searchable in 2006 records.
For information about IC= index changes, see HELP NEWSIPCR.
  File 349:PCT FULLTEXT 1979-2007/UB=20070503UT=20070426
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*File 349: For important information about IPCR/8 and forthcoming
changes to the IC= index, see HELP NEWSIPCR.
  File   5:Biosis Previews(R) 1926-2007/Apr W5
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*File   5: BIOSIS has been enhanced with archival data. Please see
HELP NEWS 5 for information.
  File  73:EMBASE 1974-2007/May 04
         (c) 2007 Elsevier B.V.
  File 399:CA SEARCH(R) 1967-2007/UD=14620
         (c) 2007 American Chemical Society
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Bacterial Toxins

Methods and Protocols
March 2000

pps. 219-240

ISBN13: 978-1-59259-052-0
ISBN10: 1-59259-052-7
Series: Methods in Molecular Biology
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Peter Amersdorfer
James D. Marks

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Abstract:
The biotechnologi generation of high affin monoclonal antibodies (MAt has traditionally involved t production of hybridomas fr spleen cells of immuniz animals (1). This eve together with availability increasingly sophisticat molecular biology and prot engineering techniqu opened up the field numerous applications a benefits in not only t medical but also industr world. Now the use of pha antibodies offers a new ro for the generation antibodies, includi antibodies of human orig which cannot be eas obtained by conventio hybridoma technology. Rec advances in the expression antibody fragments in E. c (2,3) and the application the polymerase chain reacti (4) for cloning immunoglobulin DNA (5, have mainly contributed these achievements. W phage display, antibodies c be made completely in vit bypassing the immune syst and the immunizati procedures.

Keywords:

Language: English

Crit Rev Immunol. 1999;19(3):219-60. Links

Structure, activity, and immune (T and B cell) recognition of botulinum neurotoxins.

Atassi MZ, **Oshima M**.

Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77030, USA.

Botulism, which was first reported over a century ago, is caused by botulinum neurotoxins produced by Clostridium botulinum in seven immunological serotypes (A through G). The primary structures of a number of these BoNTs have been determined and are reviewed here, together with their gene structure and synthesis. The biological actions of BoNTs, which result in their ability to block neurotransmitter release have been the subject of intensive study, and in this review we discuss the binding of BoNTs to the cell surface as well as the mechanism of their intercellular action. The ability of BoNTs to block neurotransmitter release has been exploited in therapeutic applications to reduce muscle hyperactivity for the treatment of a variety of clinical conditions associated with involuntary muscle spasm and contractions. The advantages, limitations, and risks of these applications are discussed. Certain compounds provide some limited protection against BoNT. However, more effective protection has been obtained immunologically either by passive immunity (i.e., by administration of anti-BoNT Abs) or by immunization with inactivated toxin. More recently, excellent protection has been obtained by immunization with the receptor-binding region comprising the C-terminal (residues 860 to 1296) fragment (Hc) of the heavy chain of BoNT/A. Here we review the mapping of the epitopes on the Hc region of BoNT/A that are recognized by anti-BoNT/A Abs raised in horse, human, and mouse. The epitopes on the Hc that are recognized by anti-Hc Abs and by Hc-primed T lymphocytes were mapped in two mouse strains [BALB/c (H-2d) and SJL (H-2s)]. The peptides, which contain Ab or T cell epitopes (or both) on the Hc, were used as immunogens in BALB/c and SJL mice and we identified those peptides whose Ab and/or T-cell response cross-react with Hc. Identification of these peptides is an important first step in the intricate requirements for the design of a synthetic vaccine.

PMID: 10422600 [PubMed - indexed for MEDLINE]

UTILITY
Rescue agents for treating botulinum toxin intoxications
Inventor: Li, Shengwen, Irvine, CA, US
Aoki, Kei Roger, Coto de Caza, CA, US
Steward, Lance E., Irvine, CA, US
Francis, Joseph, Aliso Viejo, CA, US
Assignee: Allergan, Inc., (02), Irvine, CA, US
Examiner: Kam, Chih-Min
Legal Representative: Stathakis, Dean G.; German, Joel B.; Voet, Martin A.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 7172764	B2	20070206	US 2003715810	20031117
Related Publ	US 20050106182	A1	20050519		

Fulltext Word Count: 18335

Summary of the Invention:

...polyclonal antibodies and/or His-tag antibodies that recognize specific amino acid sequences within the %botulinum% toxin A type protein sequence or %epitope% tags for confirmation that the iBoNT/A has in fact been processed and glycosylated in...

6104295
Derwent Accession: 2005-365766
UTILITY
Rescue agents for treating botulinum toxin intoxications
Inventor: Li, Shengwen, Irvine, CA, US
Aoki, Kei Roger, Coto de Caza, CA, US
Assignee: Unassigned
Correspondence Address: COZEN O'CONNOR, P.C., 1900 MARKET STREET, PHILADELPHIA, PA, 19103-3508, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20050106182	A1	20050519	US 2003715810	20031117

Fulltext Word Count: 19634

Description of the Invention:

...polyclonal antibodies and/or His-tag antibodies that recognize specific amino acid sequences within the %botulinum% toxin A type protein sequence or %epitope% tags for confirmation that the iBoNT/A has in fact been processed and glycosylated in...

0005788942
Derwent Accession: 2004-652009
Therapeutic monoclonal antibodies that neutralize botulinum neurotoxins
Inventor: Marks, James, INV
Amersdorfer, Peter, INV
Assignee: The Regents of the University of Carlifornia(02)
Correspondence Address: QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C., P O BOX 458, ALAMEDA, CA, 94501, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040175385	A1	20040909	US 2003632706	20030801
CIP	PENDING			US 98144886	19980831
Provisional				US 60-400721	20020801

Fulltext Word Count: 38290

Abstract:
This invention provides antibodies that specifically bind to and neutralize %botulinum% neurotoxin type A (BoNT/A) and the %epitopes% bound by those antibodies. The antibodies and derivatives thereof and/or other antibodies that specifically bind to the neutralizing %epitopes% provided herein can be used to neutralize %botulinum% neurotoxin and are therefore also useful in the treatment of botulism...

Summary of the Invention:
...0007] This invention provides novel antibodies that specifically bind to and neutralize %botulinum% neurotoxin type A (BoNT/A). In addition, the %epitopes% bound by these antibodies are provided. The antibodies and %epitopes% identified herein are suitable for the creation of fully human, or humanized (chimeric) whole (polyclonal...

...or antibody fragments. In addition the antibodies and/or variants thereof are useful in neutralizing %botulinum% neurotoxin type A and can be used to mitigate or eliminate symptoms of botulism...

...Thus, in one embodiment, this invention provides an isolated antibody that specifically binds to an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...clone 3-8, clone 3-10, and clone ING1. The antibody binds to and neutralizes %botulinum% neurotoxin type A (BoNT/A). The antibody can be of virtually any mammalian animal type...

...a specificity and affinity such that they specifically binds to binds to and neutralizes the %botulinum% neurotoxin type A. The methods can further involve contacting the BoNT/A with a second...

...0012] This invention also provides BoNT/A-neutralizing %epitopes%. Preferred %epitopes% are BoNT/A H[sub]C %epitopes% specifically bound by an antibody expressed by clone S25, clone C25, clone C39, clone 1C6...

...0013] This invention also provides methods of making a %botulinum% neurotoxin type A antibody (anti-BoNT/A) that neutralizes BoNT/A. The methods involve contacting a plurality of antibodies with an %epitope% specifically bound by an antibody expressed one or more of clone S25, clone C25, clone...

...clone 3-1, clone 3-8, clone 3-10, and/or clone ING1. Particularly preferred %epitopes% are polypeptides that are not a full-length BoNT/A and more particularly preferred polypeptides...

Description of the Invention:

...0046] In another embodiment this invention provides the %epitopes% specifically bound by %botulinum% neurotoxin type A neutralizing antibodies. These %epitopes% can be used to isolate, and/or identify and/or screen for other antibodies BoNT...kinetics, and in vitro toxin neutralization were determined for one representative scFv binding to each %epitope%. For each %epitope%, the scFv chosen for further study had the best combination of high expression level and slow k[sub]off, as determined during %epitope% mapping studies. K[sub]d for the four scFv studied ranged between 7.3X10[sup...

...the highest affinity (K[sub]d=1.1X10[sup]-9 M) reported for an anti-%botulinum% toxin antibody. k[sub]on differed over 84-fold, and...with recombinant BoNT/A binding domain (H[sub]C) and from humans immunized with pentavalent %botulinum% toxoid (Amersdorfer et al. (1997) Infect. Immun. 65: 3743-3752; Amersdorfer et al. (2002) Vaccine...

...100 unique mAbs from these libraries, three groups of scFv were identified that bound nonoverlapping %epitopes% on BoNT/AH[sub]C and that neutralized toxin in vitro (prolonged the time to...
...Vaccine 20: 1640-1648). In vitro toxin neutralization increased significantly when two scFv binding nonoverlapping %epitopes% were combined. In vivo toxin neutralization could not be determined because of the rapid clearance...0257] Understanding the antibody response in %botulinum% intoxication is important for vaccine design and passive prophylaxis. To investigate this activity, we have studied the immune response to BoNT/A (%botulinum% neurotoxin serotype A) binding domain (H[sub]C) at the molecular level using phage display...

...antibodies were isolated from V-gene repertoires prepared from (a) human volunteer immunized with pentavalent %botulinum% toxoid and (b) non-immune human peripheral blood lymphocytes and spleenocytes. A large panel of serotype specific phage expressing %botulinum% binding scFv could be selected from both libraries. %Epitope% mapping of immune scFv binders towards BoNT/A HC revealed surprisingly a limited number of scFv recognizing conformational %epitopes% that corresponded to two distinct groups, clusters I and II. Only scFv from cluster I...

...library could be conveniently grouped into clusters III-XI and appeared to share no overlapping %epitopes% with cluster I or II. In addition they showed no neutralization of toxin at biologically significant concentrations. We therefore suggest that a vaccine based on the pentavalent %botulinum% toxoid directs the humoral immune response to a limited number of immunodominant %epitopes% exposed on the binding domain HC...

...63:2738-2742; Byrneet al. (1998) Infect Immun., 66: 10). Equine plasma-derived polyclonal anti-%botulinum% antibody preparations (equine HIG) have been administered to more than 80% of adult botulism patients ...

...jr, editor. Biomedical aspects of botulism. New York: Academic Press). The large number of different %epitopes% recognized by polyclonal antibody preparations normally ensures the presence of protective antibodies, which are usually...

...from immunized mice, we identified two sets of monoclonal which bound two non-overlapping neutralizing %epitopes% on BoNT/A HC (Amersdorfer et al. (1997) Infect. Immun., 65:3743-3752). In the...

...antibodies selected from a phage antibody library constructed from a human volunteer immunized with pentavalent %botulinum% toxoid (A-E). The affinities and %epitopes% recognized by these monoclonal antibodies were compared to affinities and %epitopes% recognized by monoclonal antibodies

selected from a non-immune human phage library. The results identify an additional neutralizing %epitope% and provide a path to generating a fully human antibody for botulism prevention and treatment...

...humoral immune response in mice and human resulted in a rather limited number of protective %epitopes%, suggests significant conservation of antigenic %epitopes% conferring protection. The selection procedure involved panning both combinatorial libraries against four immobilized %botulinum% neurotoxins, serotypes A, B, C, and E. After three to four panning cycles, antibodies against...

...Clin Microbiol., 26:2351-2356), where they studied serum specimens from 25 human recipients of %botulinum% pentavalent toxoid. Immunogenicity of the various serotypes was determined by a mouse serum neutralization bioassay...

Exemplary or Independent Claim(s):

1. An isolated antibody that specifically binds to an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...3-8, clone 3-10, and clone ING1, wherein said antibody binds to and neutralizes %botulinum% neurotoxin type A (BoNT/A...

...a specificity and affinity such that it specifically binds to binds to and neutralizes said %botulinum% neurotoxin type A...

...80. A polypeptide comprising %botulinum% neurotoxin type A (BoNT/A) neutralizing %epitope%, said neutralizing %epitope% comprising an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...8, clone 3-10, and clone ING1, wherein said polypeptide is not a full-length %botulinum% neurotoxin H[sub]c fragment...

...97. A method of making a %botulinum% neurotoxin type A antibody (anti-BoNT/A) that neutralizes BoNT/A, said method comprising: contacting a plurality of antibodies with a an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...clone 3-10, and clone ING1; and isolating an antibody that specifically binds to said %epitope%.

...

...116. A composition comprising a plurality of anti-%botulinum% neurotoxin antibodies, wherein each antibody is specific for a different %epitope% of a %botulinum% neurotoxin, and wherein said combination of antibodies shows greater toxin neutralization than the single antibodies...

...118. A method of neutralizing a %botulinum% neurotoxin, said method comprising contacting said neurotoxin with a plurality of anti-%botulinum% neurotoxin antibodies, wherein each antibody is specific for a different %epitope% of said %botulinum% neurotoxin, and wherein said combination of antibodies shows greater toxin neutralization than the single antibodies

Non-exemplary or Dependent Claim(s):

...60. The method of claim 58, further comprising contacting said %botulinum% neurotoxin type A with a second anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody, said antibody comprising a variable heavy (V[sub...

...a specificity and affinity such that it specifically binds to binds to and neutralizes said %botulinum% neurotoxin type A, wherein said second anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody binds to a different %epitope% than said first anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody...

0005100357 **IMAGE Available
Derwent Accession: 2003-182618
THERAPEUTIC MONOCLONAL ANTIBODIES THAT NEUTRALIZE BOTULINUM NEUROTOXINS
Inventor: JAMES D. MARKS, INV
PETER AMERSDORFER, INV
Correspondence Address: LAW OFFICES OF JONATHAN ALAN QUINE, P O BOX 458, ALAMEDA, CA, 94501

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20020155114	A1	20021024	US 98144886	19980831

Fulltext Word Count: 27036

Abstract:
This invention provides antibodies that specifically bind to and neutralize %botulinum% neurotoxin type A (BoNT/A) and the %epitopes% bound by those antibodies. The antibodies and derivatives thereof and/or other antibodies that specifically bind to the neutralizing %epitopes% provided herein can be used to neutralize %botulinum% neurotoxin and are therefore also useful in the treatment of botulism...

Summary of the Invention:
...0007] This invention provides novel antibodies that specifically bind to and neutralize %botulinum% neurotoxin type A (BoNT/A). In addition, the %epitopes% bound by these antibodies are provided. The antibodies and %epitopes% identified herein are suitable for the creation of fully human, or humanized (chimeric) whole (polyclonal...

...or antibody fragments. In addition the antibodies and/or variants thereof are useful in neutralizing %botulinum% neurotoxin type A and can be used to mitigate or eliminate symptoms of botulism...

...Thus, in one embodiment, this invention provides an isolated antibody that specifically binds to an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...clone C25, clone C39, clone 1C6, and clone 1F3. The antibody binds to and neutralizes %botulinum% neurotoxin type A (BoNT/A). The antibody can be of virtually any mammalian animal type...

...a specificity and affinity such that they specifically binds to binds to and neutralizes the %botulinum% neurotoxin type A. The methods can further involve contacting the BoNT/A with a second...

...0012] This invention also provides BoNT/A-neutralizing %epitopes%. Preferred %epitopes% are BoNT/A Hc %epitopes% specifically bound by an antibody expressed by clone S25, C25, C39, 1C6, or 1F3. Particularly...

...0013] This invention also provides methods of making a %botulinum% neurotoxin type A antibody (anti-BoNT/A) that neutralizes BoNT/A. The methods involve contacting a plurality of antibodies with an %epitope% specifically bound by an antibody expressed one or more of clones S25, C25, C39, 1C6, or 1F3. Particularly preferred %epitopes% are polypeptides that are not a full-length BoNT/A and more particularly preferred polypeptides are not a full-length BoNT/A H[sub]c fragment. Thus, most preferred %epitopes% are a BoNT/A H[sub]C subsequence or fragment with preferred subsequences having a...

Description of the Invention:
...0046] In another embodiment this invention provides the %epitopes% specifically bound by %botulinum% neurotoxin type A neutralizing

antibodies. These %epitopes% can be used to isolate, and/or identify and/or screen for other antibodies BoNT...kinetics, and in vitro toxin neutralization were determined for one representative scFv binding to each %epitope%. For each %epitope%, the scFv chosen for further study had the best combination of high expression level and slow k[sub]off, as determined during %epitope% mapping studies. K[sub]d for the four scFv studied ranged between 7.3X10[sup...

...the highest affinity (K[sub]d=1.1X10[sup]-9 M) reported for an anti-%botulinum% toxin antibody. k[sub]on differed over 84-fold, and k[sub]off differed over...

...8 M scFv. Values are reported in time to 50% twitch reduction. scFv binding to %epitope% 1 (S25) and %epitope% 2 (C25) significantly prolonged the time to neuroparalysis: 1.5-fold (152%) and 2.7...

Exemplary or Independent Claim(s):

1. An isolated antibody that specifically binds to an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...C25, clone C39, clone 1C6, and clone 1F3, wherein said antibody binds to and neutralizes %botulinum% neurotoxin type A (BoNT/A...

...24. An isolated anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody, said antibody comprising a variable heavy (V[sub...

...a specificity and affinity such that it specifically binds to binds to and neutralizes said %botulinum% neurotoxin type A...

...64. A polypeptide comprising %botulinum% neurotoxin type A (BoNT/A) neutralizing %epitope%, said neutralizing %epitope% comprising an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...clone C39, clone 1C6, and clone 1F3, wherein said polypeptide is not a full-length %botulinum% neurotoxin H[sub]c fragment...

...70. A method of making a %botulinum% neurotoxin type A antibody (anti-BoNT/A) that neutralizes BoNT/A, said method comprising: contacting a plurality of antibodies with a an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...C39, clone 1C6, and clone 1F3; and isolating an antibody that specifically binds to said %epitope%.

Non-exemplary or Dependent Claim(s):

...43. The antibody of claim 24, wherein antibody specifically binds to an %epitope% specifically bound by an antibody expressed by a clone selected from the group consisting of...

...45. The method of claim 44, further comprising contacting said %botulinum% neurotoxin type A with a second anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody, said antibody comprising a variable heavy (V[sub...

...a specificity and affinity such that it specifically binds to binds to and neutralizes said %botulinum% neurotoxin type A, wherein said second anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody binds to a different %epitope% than said first anti-%botulinum% neurotoxin type A (anti-BoNT/A) antibody...

0005385989
Derwent Accession: 2004-031987
Protective peptides neurotoxin of C. botulinum
Inventor: Dertzbaugh, Mark, INV
Correspondence Address: Elizabeth Arwine Office of Command Judge Advocate, Fort Detrick, Frederick, MD, 21702-5012, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030185850	A1	20031002	US 2001917791	20010731
CIP	US 6287566			US 95446114	19950519

Fulltext Word Count: 4844

Summary of the Invention:

...0001] This invention relates to immunization against toxic effect of neurotoxins of Clostridium bolutinum. Protective %epitopes% of the heavy chain of the neurotoxin of C. %botulinum% have been discovered. The invention also relates to preparation of protective immunotoxins of C. %botulinum%.

4039395
Derwent Accession: 1998-520131
Utility
REASSIGNED, EXPIRED
C/ Neutralizing monoclonal antibody against botulinum neurotoxin serotype F
Inventor: Brown, Douglas Richard, 8917 N. Westland, Gaithersburg, MD, 20877
Schmidt, James Jude, 5819 Catoctia Vists, Mount Airy, MD, 21771
Assignee: Unassigned
Unassigned Or Assigned To Individual (Code: 68000)
Examiner: Feisee, Lila (Art Unit: 186)
Assistant Examiner: Reeves, Julie E.
Combined Principal Attorneys: Moran, John F.; Pratt, Sana A.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 5807741	A	19980915	US 95504969	19950720

Fulltext Word Count: 5472

Summary of the Invention:

...react with the toxin and which will be protective. Priming the immune response with irrelevant %epitopes% will predispose the immune response to those %epitopes%, even in the event the animal is later boosted with native toxin. We believe it is necessary to avoid priming the immune system to toxoided %epitopes% of the %botulinum% neurotoxin. We avoided mis-directed immune responses by immunizing with increasing sub-lethal doses of the native toxins. This is the first instance of immunizing against %botulinum% toxin using only active %botulinum% toxin as an immunogen. Furthermore, we began with %botulinum% neurotoxin serotype E, which can be purified in a single chain form (BNT/Esc) which ...

...Yet another object of the present invention is to provide an antigenic neutralizing %epitope% by mapping the antigenic determinant recognized by the monoclonal antibody of the present invention, said antigenic determinant being common to all the %botulinum% neurotoxin serotypes. Such an %epitope% would be useful for designing a vaccine protective against all the seven serotypes of %botulinum%.

Description of the Invention:

...invention is useful as a reagent for research related to the structure and function of %botulinum% neurotoxins. The exquisite specificity as well as its ability to neutralize BNT/F allows it to be used for immunochemical and structure-activity analyses of Clostridia %botulinum% neurotoxins. Mapping of the antigenic %epitope% recognized by the monoclonal antibody of the present invention will lead to the identification of similar %epitopes% present on other serotypes of %botulinum%, and the development of a vaccine protective against all the seven serotypes of %botulinum% neurotoxin...

...Mapping of the antigenic %epitope% can be accomplished by several methods known to people in the art, one of which...

...F by ELISA and on native blots. Either technique can be employed to define the %epitope%. The first step is to determine which chain, light or heavy, mAb 7F8.G2.H3...

2/3,KWIC/161 (Item 96 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

4402203
Derwent Accession: 2001-030940
Utility
C/ Assay for detecting the presence of botulinum toxin neutralizing antibodies in a patient serum sample
; IMMUNOASSAY
Inventor: Aoki, Kei Roger, Laguna Hills, CA
Spanoyannis, Athena F., Tustin, CA
Assignee: ALLERGAN, Inc.(02), Irvine, CA
Allergan Inc (Code: 20795)
Examiner: Minnifield, Nita (Art Unit: 165)
Assistant Examiner: Baskar, Padma
Combined Principal Attorneys: Hackler, Walter A.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6136551	A	20001024	US 9844194	19980317
CIP	US 5731161	A		US 95426796	19950424

Fulltext Word Count: 8768

Description of the Invention:
...It should also be appreciated that the present invention, utilizing non-SDS, non-trypsinized complex %botulinum% toxin may be practiced in "dot blotting". that is, an antigen in solution can be...

...extract to use for a western blot or used to determine whether or not the %epitope% of interest will survive the western blotting procedure...

6657220
Derwent Accession: 2002-575192
UTILITY
Recombinant vaccine against botulinum neurotoxin
Inventor: Smith, Leonard A., Clarksburg, MD, US
Byrne, Michael P., New Market, MD, US
Middlebrook, John L., Middletown, MD, US
Lapenotiere, Hugh, Charlestown, WV, US
Clayton, Michael A., Mt. Airy, MD, US
Brown, Douglas R., Githersburg, MD, US
Assignee: The United States of America as represented by the Secretary of the Army, (06), Washington, DC, US
Examiner: Smith, Lynette R. F.
Assistant Examiner: Portner, Ginny Allen
Legal Representative: Arwine, Elizabeth

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 7081529	B2	20060725	US 2001910186	20010720
Related Publ	US 20030009025	A1	20030109		
Continuation	PENDING			US 2000611419	20000706
Continuation	PENDING			WO 2000US12890	20000512
CIP	ABANDONED			US 93123975	19930921
Provisional				US 60-146192	19990729
Provisional				US 60-133866	19990512
Provisional				US 60-133868	19990512
Provisional				US 60-133869	19990512
Provisional				US 60-133865	19990512
Provisional				US 60-133873	19990512
Provisional				US 60-133867	19990512

Fulltext Word Count: 14140

Abstract:
...This invention is directed to preparation and expression of synthetic genes encoding polypeptides containing protective %epitopes% of %botulinum% neurotoxin (BoNT). The invention is also directed to production of immunogenic peptides encoded by the...

Summary of the Invention:
...This invention is directed to preparation and expression of synthetic genes encoding polypeptides containing protective %epitopes% of %botulinum% neurotoxin (BoNT). The invention is also directed to methods of vaccination against botulism using the...0024] In still another embodiment, this invention provides an immunogenic composition comprising a polypeptide comprising %epitopes% contained in the carboxy-terminal portion of the heavy chain (HC) of %botulinum% neurotoxin (BoNT) and/or the amino-terminal portion of the heavy chain (HN) of %botulinum% neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT...

...BoNT serotype D, BoNT serotype E, BoNT serotype F, and/or BoNT serotype G, said %epitopes% eliciting protective immunity toward the respective BoNT serotype. Preferably, the immunogenic composition elicits an ELISA ...

...present inventors have determined that animals, including primates, may be protected from the effects of %botulinum% neurotoxin (BoNT) by immunization with fragments of the %botulinum% neurotoxin protein expressed by recombinant organisms. Specifically, peptides comprising protective %epitopes% from the receptor binding domain and/or the translocation domain, found in the carboxy terminal...plasmids and

recombinant proteins for use as vaccines to provide protection against toxins of Clostridium %botulinum%.

[...

...Botulism Neurotoxin", L. L. Simpson, ed., 1989, Academic Press, New York) suggested that a protective %epitope% might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson...herein in their entirety by reference) deduced the amino acid sequence for the serotype A %botulinum% toxin. DasGupta et al. (1990, Biochemie, 72:661-664) identified the "nick" site for post...0058] Synthetic genes for the H[sub]C fragments of %botulinum% neurotoxin serotypes A-G are shown in FIGS. 1-10, along with the amino acid sequences encoded by the synthetic genes. Synthetic genes for the H[sub]N fragments of %botulinum% neurotoxin serotypes A-G are shown in FIGS. 11-17, along with the amino acid...

...sequence of one of the BoNT serotype proteins, or a fragment thereof which contains protective %epitopes%. Suitable fragments include the H[sub]C fragments of BoNT serotypes A, B C[sub...
...0059] Also within the contemplation of this invention are proteins containing protective %epitopes% from both the N-terminal and the C-terminal domains of the respective serotype BoNT...other nucleotides on the 5' end of the gene that are not part of the %botulinum% toxin gene. Then a common restriction enzyme site not found in either synthetic gene may...

UTILITY

Recombinant vaccine against botulinum neurotoxin

Inventor: Smith, Leonard A., Clarksburg, MD, US
Byrne, Michael P., New Market, MD, US
Middlebrook, John L., Middletown, MD, US
Lapenotiere, Hugh, Charlestown, WV, US
Clayton, Michael A., Mt. Airy, MD, US
Brown, Douglas R., Gaithersburg, MD, US
Assignee: Unassigned
Correspondence Address: BAKER & BOTTS L.L.P., 30 ROCKEFELLER PLAZA, 44TH FLOOR, NEW YORK, NY, 10112-4498, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20070037257	A1	20070215	US 2006437212	20060519
Division	US 7081529			US 2001910186	20010720
Continuation	ABANDONED			US 2000611419	20000706
Continuation	PENDING			WO 2000US12890	20000512
CIP	ABANDONED			US 93123975	19930921
Provisional				US 60-133866	19990512
Provisional				US 60-133873	19990512
Provisional				US 60-133869	19990512
Provisional				US 60-133865	19990512
Provisional				US 60-133868	19990512
Provisional				US 60-133867	19990512
Provisional				US 60-146192	19990729

Fulltext Word Count: 16076

Abstract:

...This invention is directed to preparation and expression of synthetic genes encoding polypeptides containing protective %epitopes% of %botulinum% neurotoxin (BoNT). The invention is also directed to production of immunogenic peptides encoded by the...

Summary of the Invention:

...This invention is directed to preparation and expression of synthetic genes encoding polypeptides containing protective %epitopes% of %botulinum% neurotoxin (BoNT). The invention is also directed to methods of vaccination against botulism using the...0024] In still another embodiment, this invention provides an immunogenic composition comprising a polypeptide comprising %epitopes% contained in the carboxy-terminal portion of the heavy chain (H[sub]C) of %botulinum% neurotoxin (BoNT) and/or the amino-terminal portion of the heavy chain (H[sub]N) of %botulinum% neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT...

...BoNT serotype D, BoNT serotype E, BoNT serotype F, and/or BoNT serotype G, said %epitopes% eliciting protective immunity toward the respective BoNT serotype. Preferably, the immunogenic composition elicits an ELISA ...

Description of the Invention:

...present inventors have determined that animals, including primates, may be protected from the effects of %botulinum% neurotoxin (BoNT) by immunization with fragments of the %botulinum% neurotoxin protein expressed by recombinant organisms. Specifically, peptides comprising protective %epitopes% from the receptor binding domain and/or the translocation domain, found in the carboxy terminal...plasmids and recombinant proteins for use as vaccines to provide protection against toxins of Clostridium %botulinum%.

[...

...Botulism Neurotoxin," L. L. Simpson, ed., 1989, Academic Press, New York) suggested that a protective %epitope% might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson...

...herein in their entirety by reference) deduced the amino acid sequence for the serotype A %botulinum% toxin. DasGupta et al. (1990, Biochemie, 72:661-664) identified the "nick" site for post...0057] Synthetic genes for the H[sub]C fragments of %botulinum% neurotoxin serotypes A-G are shown in FIGS. 1-10, along with the amino acid sequences encoded by the synthetic genes. Synthetic genes for the H[sub]N fragments of %botulinum% neurotoxin serotypes A-G are shown in FIGS. 11-17, along with the amino acid...

...sequence of one of the BoNT serotype proteins, or a fragment thereof which contains protective %epitopes%. Suitable fragments include the H[sub]C fragments of BoNT serotypes ...0058] Also within the contemplation of this invention are proteins containing protective %epitopes% from both the N-terminal and the C-terminal domains of the respective serotype BoNT...

...other nucleotides on the 5' end of the gene that are not part of the %botulinum% toxin gene. Then a common restriction enzyme site not found in either synthetic gene may...

Exemplary or Independent Claim(s):

...32. An immunogenic composition comprising at least a portion of the heavy chain of a %botulinum% neurotoxin serotype selected from the group consisting of serotype B, serotype C[sub]1, serotype...

...37. A nucleic acid sequence encoding a protein comprising at least one %epitope% of the amino-terminal portion or the carboxy-terminal portion of the heavy chain of a %botulinum% neurotoxin serotype selected from the group consisting of serotype B, serotype C[sub]1, serotype...

Non-exemplary or Dependent Claim(s):

...The immunogenic composition of claim 32, wherein said portion of the heavy chain of a %botulinum% neurotoxin serotype elicits an ELISA response to the corresponding %botulinum% neurotoxin serotype in an animal, said ELISA response being detectable upon about 100-fold dilution...

...34. The immunogenic composition of claim 32, wherein said portion of a %botulinum% neurotoxin serotype comprises at least one %epitope% of the amino-terminal portion or the carboxy-terminal portion of the heavy chain of a %botulinum% neurotoxin serotype selected from the group consisting of serotype B, serotype C[sub]1, serotype D, serotype E, serotype F, and serotype G, wherein said %epitope% is capable of eliciting protective immunity toward the corresponding %botulinum% neurotoxin serotype...

...immunogenic composition of claim 34, wherein said immunogenic composition elicits an ELISA response to a %botulinum% neurotoxin serotype in an animal, said ELISA response

TILITY
C/ Type F botulinum toxin and use thereof
; POLYPEPTIDE FREE OF BOTULINUM TOXIN ACTIVITY AND FREE OF TOXOID WHICH INDUCES PROTECTIVE IMMUNITY TO A TYPE F BOTULINUM TOXIN; VACCINES; FUSION PROTEIN WITH POLYPEPTIDE FOR ENHANCED CHROMATOGRAPHIC PURIFICATION

Inventor: Elmore, Michael J., Basingstoke, GB
Mauchline, Margaret L., Shaftesbury, GB
Minton, Nigel P., Salisbury, GB
Pasechnik, Vladimir A., Shrewton, GB
Titball, Richard W., Durrington, GB
Assignee: Microbiological Research Authority, (03), Wiltshire, GB
Microbiological Research Authority GB (Code: C07K-0001/00 _A_I_F_B_20060101_20060509_H_US)
Examiner: Saoud, Christine J.
Assistant Examiner: Turner, Sharon L.
Legal Representative: Nixon & Vanderhye PC

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 7041792	B2	20060509	US 96981087	19960612
Related Publ	US 20020081304	A1	20020627		
PCT	WO 9641881	A	19961227	WO 96GB1409	19960612
Priority				GB 9511909	19950612

US Term Extension: 331 days

Fulltext Word Count: 5294

Summary of the Invention:

...invention provides a peptide or peptide conjugate comprising the amino acid sequence of the C. %botulinum% strain Langeland BoNT/F from amino acids 848 to 1278 (SEQ ID NO:1), but lacking the amino acid sequences of the L chain and H[sub]N %epitopes% necessary for metalloprotease activity and toxin internalisation (found between amino acids 1 to 439 and...

Derwent Accession: 2002-575196
UTILITY
Vaccine based on a cellular penetration factor from an apicomplexan parasite
Inventor: Gillespie, Stephen Henry, London, GB
Bayele, Henry Kean, London, GB
McHugh, Timothy Daniel, London, GB
Assignee: Unassigned
Correspondence Address: Pillsbury Winthrop;Intellectual Property Group, PO Box 10500, McLean, VA, 22102, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20050260224	A1	20051124	US 2001416384	20011109
PCT	WO 2001GB4985		20011109		
Priority				GB 200027433	20001109

Fulltext Word Count: 16182
Description of the Invention:
...Richard W. Titball.Cloning, expression and evaluation of a recombinant sub-unit vaccine against Clostridium %botulinum% type. F toxin [Abstract] [Full text] Vaccine 19 (2-3) 288-297 (20000137] Michael Theisen et al. Identification of a major B-cell %epitope% of the Plasmodium falciparum glutamate-rich protein (GLURP), targeted by human antibodies mediating parasite killing...

6333810 **IMAGE Available
Derwent Accession: 1998-230234
UTILITY
C/ Soluble recombinant botulinum toxin proteins
; EXPRESSING A BOTULINUM TOXIN FROM A PROKARYOTIC EXPRESSION VECTOR COMPRISING A BOTULINUM TOXIN NUCLEOTIDE SEQUENCE IN A PROKARYOTIC HOST CELL WHEREIN THE PROKARYOTIC EXPRESSION VECTOR IS T7LAC PROMOTER
Inventor: Williams, James A., Lincoln, NE, US
Thalley, Bruce S., Madison, WI, US
Assignee: Allergan, Inc., (02), Irvine, CA, US
Allergan Botox Limited, (02), Irvine, CA, US
Allergan Botox Ltd
Allergan Inc (Code: 20795 71351)
Examiner: Housel, James
Assistant Examiner: Li, Bao Qun
Legal Representative: Hollrigel, Greg S.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6967088	B1	20051122	US 96704159	19960828
CIP	US 5919665	A		US 95405496	19950316

Fulltext Word Count: 82400

Summary of the Invention:

...SEQ ID NO:40; this fusion protein thus comprises the receptor-binding domain for C. %botulinum% type B toxin as defined above (i.e., Ile-848 through Glu-1291). Similarly, pHisBotE...expression vector, said vector encoding a protein comprising at least a portion of a Clostridium %botulinum% toxin, said toxin selected from the group consisting of type B toxin and type E...

...present invention is not limited by the nature of sequences encoding portions of the C. %botulinum% toxin. These sequences may be derived from the native gene sequences or alternatively they may...of patients effected by or at risk of symptoms due to the action of C. %botulinum% toxins. The organisms, toxins and individual steps of the present invention are described separately below...11, demonstrate almost complete neutralization of toxin A using the affinity purified (AP) mix. Some %epitopes% within the recombinant proteins utilized for affinity purification were probably lost when the proteins were...the mixture was administered to hamsters via IP injection. If the recombinant protein contains neutralizing %epitopes%, the CTA antibodies would lose their ability to bind toxin A resulting in diarrhea and...

Ultrasensitive biochemical sensing platform
Inventor: Holm-Kennedy, James W., Honolulu, HI, US
Assignee: Unassigned
Correspondence Address: JAMES C. WRAY, 1493 CHAIN BRIDGE ROAD, SUITE 300, MCLEAN, VA, 22101, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20050224346	A1	20051013	US 2004976503	20041029
Provisional				US 60-516485	20031031
Provisional				US 60-516535	20031031

Fulltext Word Count: 16909

Description of the Invention:

...example, the sensor may comprise two or more antibodies to a particular antigen, such as %botulinum% toxin. When two or more antibodies are used, each antibody preferably binds to a different %epitope% on the target antigen. In another specific embodiment two or more different oligonucleotides are provided...

Derwent Accession: 2005-089574
Botulinum toxin a peptides and methods of predicting and reducing immunoresistance to botulinum toxin therapy
Inventor: Atassi, M., INV
Correspondence Address: MCDERMOTT, WILL & EMERY, 4370 LA JOLLA VILLAGE DRIVE, SUITE 700, SAN DIEGO, CA, 92122, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040265935	A1	20041230	US 2004821669	20040409
Provisional				US 60-462754	20030411

Fulltext Word Count: 50107

Description of the Invention:

...0050] This invention relates to %botulinum% neurotoxin A (BoNT/A) peptides that represent the complete repertoire of %epitopes% from the H[sub]N domain of BoNT/A recognized by antibodies from humans immunized with pentavalent %botulinum% toxoid. BoNT/A peptides of the invention, and antibodies that bind to such peptides, are useful, for example, in methods for predicting or diagnosing immunoresistance to %botulinum% toxin therapy, for reducing the development of such immunoresistance, and for boosting immunity against unwanted %botulinum% toxicity...

...19:219-260 (1999); Jankovic, in Brian et al., Eds., Scientific and Therapeutic Aspects of %Botulinum% Toxin, pp. 409-415, Lippincott Williams & Wilkins; Philadelphia, Pa. (2002). While all patient antibody responses...

...the patient's serum to blocking antibodies. As further disclosed herein in Example VIII, the %epitope% recognition profile was compared in inbred BALB/c and SJL mice before and after the...

...non-protective to protective antibodies. The results disclosed herein demonstrated only slight differences in the %epitope% recognition profiles of non-protective and protective antisera, indicating that changes in antibody binding may...

...and immunoreactive fragments of the amino acid sequences disclosed herein, each contain one or more %epitopes% recognized by antibodies contained in antisera from animals, for example, humans, immunized with BoNT/A. As described above, patients treated with %botulinum% toxin can develop immunoresistance to the therapeutic toxin, reducing or eliminating the beneficial effect of %botulinum% toxin therapy. The BoNT/A peptides of the invention are useful in methods of predicting or determining immunoresistance to %botulinum% toxin therapy in an individual...contained within amino acids 785-803 of SEQ ID NO:1, which correspond to the %epitope% defined within the N25 peptide. In still further embodiments, any of the monoclonal antibodies disclosed...

...a homogeneous population of antibody species. By definition, a monoclonal antibody binds to a single %epitope%.

[...

...0135] Treatment of %Botulinum% Toxicity...

...can be removed from a patient to be treated or having been treated with a %botulinum% toxin therapeutic such as BOTOX(R); and anti-%botulinum% toxin antibodies subsequently removed from the blood, serum or plasma using affinity chromatography with one...
...C20 or C31 BoNT/A peptides are used for therapeutic immunoadsorption

such that antibodies to %epitopes% in the peptides used for the immunoadsorption are removed from patient blood, serum or plasma...

...0140] Thus, the present invention provides a method of removing %botulinum% toxin blocking antibodies from a patient by removing blood from a patient; contacting the blood

0005859980 **IMAGE Available
Derwent Accession: 1998-230234
Soluble recombinant botulinum toxins having a C-terminal portion of a heavy chain, a N-terminal portion of a heavy chain and a light chain
Inventor: Williams, James, INV
Assignee: Allergan Sales, Inc. Allergan Botox Limited(02), Irvine, CA
Correspondence Address: STOUT, UXA, BUYAN & MULLINS LLP, 4 VENTURE, SUITE 300, IRVINE, CA, 92618, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040219637	A1	20041104	US 2003729527	20031205
Division	PENDING			US 2002271012	20021015
Continuation	PENDING			US 96704159	19960828
CIP	US 5919665			US 95405496	19950316

Fulltext Word Count: 85135

Description of the Invention:

...SEQ ID NO:40; this fusion protein thus comprises the receptor-binding domain for C. %botulinum% type B toxin as defined above (i.e., Ile-848 through Glu-1291). Similarly, pHisBotE...

...expression vector, said vector encoding a protein comprising at least a portion of a Clostridium %botulinum% toxin, said toxin selected from the group consisting of type B toxin and type E...

...present invention is not limited by the nature of sequences encoding portions of the C. %botulinum% toxin. These sequences may be derived from the native gene sequences or alternatively they may...

...0106] In one embodiment, the host cell is capable of expressing the recombinant C. %botulinum% toxin protein at a level greater than or equal to 2% to 40% of the...toxins HT and LT, toxins A, B, C, D, E, F, and G of C. %botulinum% and the numerous C. perfringens toxins. In one preferred embodiment, toxins A, B, and E of C. %botulinum% are contemplated as immunogens. Table 2 above lists various Clostridium species, their toxins and some...0328] This Example involved (a) %epitope% mapping of the toxin A protein to determine the titre of specific antibodies directed against...

...11, demonstrate almost complete neutralization of toxin A using the affinity purified (AP) mix. Some %epitopes% within the recombinant proteins utilized for affinity purification were probably lost when the proteins were...

...clone pPA1100-1450 in FIG. 9) are important for neutralization of cytotoxicity in this assay. %Epitope% mapping has shown that only low levels of antibodies reactive to this region are generated...loss of neutralizing capacity of the CTA antibody would indicate that those proteins contain neutralizing %epitopes%. Preimmune and CTA antibodies (both at 0.5X) without the addition of any recombinant protei

6972351
UTILITY
Escherichia coli-derived vaccine and therapy against botulism
Inventor: Baldwin, Michael, Milwaukee, WI, US
Bradshaw, Marite, Madison, WI, US
Tepp, William H., Stoughton, WI, US
Johnson, Eric A., Madison, WI, US
Barbieri, Joseph T., Milwaukee, WI, US
Pier, Christina L., Fitchouig, WI, US
Assignee: Unassigned
Correspondence Address: QUARLES & BRADY LLP, 411 E. WISCONSIN AVENUE, SUITE 2040, MILWAUKEE, WI, 53202-4497, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20070059326	A1	20070315	US 2005289851	20051130
Provisional				US 60-632502	20041202

Fulltext Word Count: 7648
Description of the Invention:

...in the United States demonstrate various acute reactions (4). The current vaccine is a pentavalent %botulinum% toxoid (A-E), which is effective but has several limitations including cost, efficacy and accessibility...

...0057] Previous studies have indicated that major protective %epitopes% of BoNT/A are located in the receptor-binding domain (HCR) (7, 25). Thus, the use of HCR/A has been included in strategies for %botulinum% antibody therapy and vaccine development. The HCR component of BoNTs has several potential advantages over currently available C. %botulinum%-derived antigens. Production of HCR in a heterologous system facilitates large scale production and removes...and coworkers have recently expressed HCR/A in E. coli and mapped the major protective %epitopes% of the BoNT to HCR (32...

...0058] The C. %botulinum% A Hall-hyper (28) has been used widely for the production of BoNT/A vaccines...0059] Classically, %botulinum% serotypes are defined by the lack of cross-protection between neutralizing anti-sera, i.e...

...hyper immunization with HCR/E to BoNT/A1 intoxication suggests the presence of cross protective %epitope%(s) within the BoNTs. The enhanced cross protection elicited by HCR/E[sub]B relative to HCR/A may be due to a polyclonal %epitope% response to the HCRs, where antibodies to multiple %epitopes% are required for neutralization (3) or may represent the expansion of a minor common %epitope% that is stimulated upon immunization with large amounts of antigen. While it is not practical...

0005501508 **IMAGE Available
Derwent Accession: 2003-722327
Immunotherapeutics for biodefense
Inventor: Bowdish, Katherine, INV
Frederickson, Shana, INV
Wild, Martha, INV
Maruyama, Toshiaki, INV
Nolan, Mary, INV
Correspondence Address: Mark Farber, Esq. Alexion Pharmaceuticals, Inc., 352 Knotter Drive, Cheshire, CT, 06410, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040009178	A1	20040115	US 2003364743	20030211
Provisional				US 60-356086	20020211
Provisional				US 60-376408	20020429
Provisional				US 60-414053	20020927
Provisional				US 60-428807	20021125

Fulltext Word Count: 15340

Summary of the Invention:
...an immunogenic response to the humanized Ab. Antibodies that are fully human and target neutralizing %epitopes% on VEEV are the most desirable therapeutic candidates, as they pose the best chance of...

...0015] %Botulinum% neurotoxin is one of the most potent bacterial toxins known, with an LD50 for humans...

Description of the Invention:
...al., (Nowakowski et al., 2002) found that a mixture of three antibodies to non-overlapping %epitopes% derived by phage display produced potent neutralization of the %botulinum% neurotoxin, where each antibody alone showed little effect...

0005156702 **IMAGE Available
Derwent Accession: 2002-575192
Recombinant vaccine against botulinum neurotoxin
Inventor: Leonard Smith, INV
Michael Byrne, INV
John Middlebrook, INV
Hugh Lapenotiere, INV
Michael Clayton, INV
Douglas Brown, INV
Correspondence Address: BAKER & BOTTS, 30 ROCKEFELLER PLAZA, NEW YORK, NY, 10112

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030009025	A1	20030109	US 2001910186	20010720
Continuation	PENDING			US 2000611419	20000706
Provisional				US 60-133866	19990512
Provisional				US 60-133868	19990512
Provisional				US 60-133869	19990512
Provisional				US 60-133865	19990512
Provisional				US 60-133873	19990512
Provisional				US 60-133867	19990512
Provisional				US 60-146192	19990729
Priority				WO 2000US12890	20000512

Fulltext Word Count: 17724

Abstract:
This invention is directed to preparation and expression of synthetic genes encoding polypeptides containing protective %epitopes% of %botulinum% neurotoxin (BoNT). The invention is also directed to production of immunogenic peptides encoded by the...

Summary of the Invention:
...This invention is directed to preparation and expression of synthetic genes encoding polypeptides containing protective %epitopes% of %botulinum% neurotoxin (BoNT). The invention is also directed to methods of vaccination against botulism using the...

...0024] In still another embodiment, this invention provides an immunogenic composition comprising a polypeptide comprising %epitopes% contained in the carboxy-terminal portion of the heavy chain (HC) of %botulinum% neurotoxin (BoNT) and/or the amino-terminal portion of the heavy chain (H[sub]N) of %botulinum% neurotoxin (BONT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT...

...BoNT serotype D, BoNT serotype E, BoNT serotype F, and/or BoNT serotype G, said %epitopes% eliciting protective immunity toward the respective BoNT serotype. Preferably, the immunogenic composition elicits an ELISA ...

Description of the Invention:
...present inventors have determined that animals, including primates, may be protected from the effects of %botulinum% neurotoxin (BONT) by immunization with fragments of the %botulinum% neurotoxin protein expressed by recombinant organisms. Specifically, peptides comprising protective %epitopes% from the receptor binding domain and/or the translocation domain, found in the carboxy terminal...

...plasmids and recombinant proteins for use as vaccines to provide protection against toxins of Clostridium %botulinum%.

[...

...Botulism Neurotoxin", L. L. Simpson, ed., 1989, Academic Press, New York, suggested that a protective %epitope% might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson...

...Eur. J. Biochem. 189:73-81) deduced the amino acid sequence for the serotype A %botulinum% toxin. DasGupta, et al. (1990, Biochemie, 72:661-664), identified the "nick" site for post...

...0058] Synthetic genes for the H[sub]C fragments of %botulinum% neurotoxin serotypes A-G are shown in FIGS. 1-10, along with the amino acid sequences encoded by the synthetic genes. Synthetic genes for the H[sub]N fragments of %botulinum% neurotoxin serotypes A-G are shown in FIGS. 11-17, along with the amino acid...

...sequence of one of the BoNT serotype proteins, or a fragment thereof which contains protective %epitopes%. Suitable fragments include the H[sub]C fragments of BoNT serotypes A, B C[sub...

...0059] Also within the contemplation of this invention are proteins containing protective %epitopes% from both the N-terminal and the C-terminal domains of the respective serotype BoNT...

...other nucleotides on the 5' end of the gene that are not part of the %botulinum% toxin gene. Then a common restriction enzyme site not found in either synthetic gene may

Exemplary or Independent Claim(s):

...immunogenic composition comprising the amino-terminal portion of the heavy chain (H[sub]N) of %botulinum% neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT...

...24. An immunogenic composition comprising a polypeptide comprising %epitopes% contained in the carboxy-terminal portion of the heavy chain (H[sub]C) of %botulinum% neurotoxin (BoNT) or the amino-terminal portion of the heavy chain (H[sub]N) of %botulinum% neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT...

...C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G, said %epitopes% eliciting protective immunity toward the respective BoNT serotype...

...26. An immunogenic composition comprising a protein containing at least a portion of a %botulinum% neurotxin (BoNT) sequence, said BoNT being selected from the group consisting of BoNT serotype A...

4568610
Derwent Accession: 2001-615462
Utility
C/ Protective peptides neurotoxin of C. botulinum
; ISOLATED POLYPEPTIDE
Inventor: Dertzbaugh, Mark T., Frederick, MD
Assignee: The United States of America as represented by the Secretary of the Army(06), Washington, DC
U S of America Army Secretary of (Code: 86528)
Examiner: Duffy, Patricia A. (Art Unit: 165)
Combined Principal Attorneys: Arwine, Elizabeth; Moran, John Francis; Harris, Charles H.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6287566	A	20010911	US 95446114	19950519

Fulltext Word Count: 4760
Summary of the Invention:
...This invention relates to immunization against toxic effect of neurotoxins of Clostridium %botulinum%. Protective %epitopes% of the heavy chain of the neurotoxin of C. %botulinum% have been discovered. The invention also relates to preparation of protective immunotoxins of C. %botulinum%.

3958442 **IMAGE Available
Derwent Accession: 1998-216490
Utility
REASSIGNED
C/ Botulinum toxin antibody detection assay
; SEPARATING TOXIN PROTEIN COMPLEX BY ELECTROPHORESIS, TRANSFERRING TOXIN TO A SOLID SUPPORT, BLOCKING REMAINING BINDING SITES ON SUPPORT, CONTACTING SUPPORT WITH HUMAN SERUM, AN ENZYME LABELED ANTIBODY AND A CHROMOGENIC SUBSTRATE
Inventor: Aoki, Kei Roger, Laguna Hill, CA
Spanoyannis, Athena Faye, Tustin, CA
Assignee: Allergan, Inc.(02), Irvine, CA
Allergan Inc (Code: 20795)
Examiner: Spiegel, Carol A. (Art Unit: 187)
Combined Principal Attorneys: Hackler, Walter A.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 5731161	A	19980324	US 95426796	19950424

Fulltext Word Count: 8746

Description of the Invention:
...It should also be appreciated that the present invention, utilizing non-SDS, non-trypsinized complex %botulinum% toxin may be practiced in "dot blotting". that is, an antigen in solution can be...

...extract to use for a western blot or used to determine whether or not the %epitope% of interest will survive the western blotting procedure...

09077255 PMID: 1723713

[The structure and function of botulinum type C neurotoxin]

Kimura K

Department of Microbiology, Sapporo Medical College, Japan.

Hokkaido igaku zasshi The Hokkaido journal of medical science (JAPAN) Nov 1991, 66 (6) p841-8, ISSN 0367-6102--Print Journal Code: 17410290R

Publishing Model Print

Document type: Journal Article ; English Abstract

Languages: JAPANESE

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

The structure gene for botulinum type C neurotoxin was cloned from the toxigenic bacteriophage obtained from Clostridium botulinum type C, and the whole nucleotide sequence was determined. The nucleotide sequence contained a single open reading frame coding for 1,291 amino acids corresponding to a polypeptide with a molecular weight of 149,000. The signal peptide was not found after the first methionine residue. Upstream of the ATG codon, sequences predicted as a Shine-Dalgarno and a promoter were found. When the deduced amino acid sequence of type C toxin was compared with those of type A and D %botulinum% toxins and tetanus toxin, type C toxin shared about 52% identity with type D toxin, but shared only about 33% identity with type A and tetanus toxins. The structure and function of type C toxin were estimated from the results of %epitope% map with monoclonal antibodies and DNA thermal stability map.

Descriptors: *Botulinum Toxins; Amino Acid Sequence; Base Sequence; %Botulinum% Toxins--chemistry--CH; %Botulinum% Toxins--genetics--GE; Codon ; DNA, Bacterial; English Abstract; %Epitopes%; Molecular Sequence Data; Molecular Weight

Molecular Sequence Databank No.: GENBANK/D90210

CAS Registry No.: 0 (Botulinum Toxins); 0 (Codon); 0 (DNA, Bacterial); 0 (Epitopes)

Record Date Created: 19920317

Record Date Completed: 19920317

08714393 PMID: 1707941

[Molecular structure and function of Clostridium botulinum neurotoxin]

Kozaki S

Department of Veterinary Science, University of Osaka Prefecture.

Seikagaku. The Journal of Japanese Biochemical Society (JAPAN) Dec 1990 , 62 (12) p1496-500, ISSN 0037-1017--Print Journal Code: 0413564

Publishing Model Print

Document type: Journal Article

Languages: JAPANESE

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Descriptors: *Botulinum Toxins--toxicity--TO; Acetylcholine--metabolism --ME; Amino Acid Sequence; Animals; %Botulinum% Toxins--metabolism--ME; %Epitopes%; Molecular Sequence Data; Molecular Structure

CAS Registry No.: 0 (Botulinum Toxins); 0 (Epitopes); 51-84-3 (Acetylcholine)

Record Date Created: 19910523

Record Date Completed: 19910523

8583084 PMID: 2213557

Use of monoclonal antibodies as probes for the structure and biological activity of botulinum neurotoxin.

Simpson L L; Kamata Y; Kozaki S

Department of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania.

Journal of pharmacology and experimental therapeutics (UNITED STATES) Oct 1990, 255 (1) p227-32, ISSN 0022-3565--Print Journal Code: 0376362

Contract/Grant No.: NS-22153; NS; NINDS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Experiments were done to help clarify the structure-function relationships that govern the interaction between %botulinum% neurotoxin and the cholinergic neuromuscular junction. Work was done with type E toxin in three different states: 1) unactivated (post-translational product before proteolytic processing), 2) activated (proteolytically modified product) and 3) denatured. Four different monoclonal antibodies were studied (E3, E14, E17 and E32), three of which were capable of diminishing the potency of the toxin. All four antibodies had approximately equivalent affinity for the unactivated and the activated forms of the toxin. Monoclonals E17 and E32 had little ability to interact with denatured toxin, suggesting they recognized conformational %epitopes%; monoclonals E3 and E14 retained partial ability to bind to denatured toxin, suggesting they recognized both conformational and linear determinants. When phrenic nerve-hemidiaphragm preparations were exposed to toxin under conditions that allowed binding but retarded internalization, the toxin remained accessible to antibodies. However, when tissues were stimulated in an effort to promote endocytosis, the toxin disappeared from accessibility to antibodies. The data indicate that various antigenic domains remain exposed after binding and suggest that certain parts of the toxin molecule undergo little or no conformational change during binding. The data further indicate that the molecular domains recognized by E14, E17 and E32 are internalized simultaneously.

Descriptors: *Antibodies, Monoclonal--diagnostic use--DU; *Botulinum Toxins--pharmacology--PD; Animals; Antibodies, Monoclonal--immunology--IM; Botulinum Toxins--chemistry--CH; Botulinum Toxins--metabolism--ME; Enzyme-Linked Immunosorbent Assay; In Vitro; Mice; Mice, Inbred BALB C; Neuromuscular Junction--drug effects--DE; Neuromuscular Junction --metabolism--ME; Protein Conformation; Research Support, U.S. Gov't, Non-P.H.S.; Research Support, U.S. Gov't, P.H.S.; Structure-Activity Relationship

CAS Registry No.: 0 (Antibodies, Monoclonal); 0 (Botulinum Toxins)

Record Date Created: 19901121

Record Date Completed: 19901121

07501318 PMID: 2824382

Antigenic structure of Clostridium botulinum type B neurotoxin and its interaction with gangliosides, cerebroside, and free fatty acids.

Kozaki S; Ogasawara J; Shimote Y; Kamata Y; Sakaguchi G

Department of Veterinary Science, College of Agriculture, University of Osaka Prefecture, Japan.

Infection and immunity (UNITED STATES) Dec 1987, 55 (12) p3051-6, ISSN 0019-9567--Print Journal Code: 0246127

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

A fragment distinct from the heavy and light chains was obtained by treatment of Clostridium %botulinum% type B neurotoxin with chymotrypsin. Enzyme-linked immunosorbent assay and immunoblotting analysis with monoclonal antibodies showed that the fragment consisted of the light chain and part of the heavy chain (H-1 fragment) linked together by a disulfide bond. Monoclonal antibodies reacting to the heavy chain but not to the fragment were thought to recognize the %epitopes% on the remaining portion (H-2 fragment) of the heavy chain, being easily digested by chymotrypsin. Thus, the antigenic structure of type B neurotoxin resembles those of type A and E neurotoxins. The chymotrypsin-induced fragment bound to cerebroside and free fatty acids but not to gangliosides. The manner of binding of type B neurotoxin to gangliosides and free fatty acids was different from those of type A and E neurotoxins. Such differences in the reactivities to lipids may be related to the finding that each neurotoxin binds to a type-specific site on the neural membrane.

Descriptors: *Botulinum Toxins--immunology--IM; *Clostridium botulinum --immunology--IM; *Neurotoxins--immunology--IM; Antibodies, Monoclonal --immunology--IM; Cerebrosides--physiology--PH; Chromatography, Thin Layer; Fatty Acids, Nonesterified--physiology--PH; Gangliosides--physiology--PH; Immunosorbent Techniques; Peptide Fragments--immunology--IM; Protein Binding; Receptors, Cell Surface--physiology--PH; Research Support, Non-U.S. Gov't

CAS Registry No.: 0 (Antibodies, Monoclonal); 0 (Botulinum Toxins); 0 (Cerebrosides); 0 (Fatty Acids, Nonesterified); 0 (Gangliosides); 0 (Neurotoxins); 0 (Peptide Fragments); 0 (Receptors, Cell Surface)

Record Date Created: 19880106

Record Date Completed: 19880106

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, May 09, 2007

Hide?	Set Name	Query	Hit Count
		DB=DWPI,JPAB,EPAB,USOC,USPT,PGPB; PLUR=YES; OP=OR	
☐	L1	(HN)!	53075
☐	L2	("H.SUB.N" | "H.SUB.NA")!	4175
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=OR	
☐	L3	(l1 or l2) same (peptide or epitope or epi-tope or fragment or polypeptide or poly-peptide or btn or botox or botulin or botulinum or botulism or tolerence or toleragen or immunotolerance or immunoresistence)	1242
☐	L4	L3 and (clostrid$ or botul$)	235
☐	L5	L4 and allergan$.asn.	82
☐	L6	geysen	5635
☐	L7	epitope near map$	5523
☐	L8	(l1 or l2) and (l6 or l7)	181
☐	L9	L8 and allergan$.asn.	9
☐	L10	l8 not l9	172
☐	L11	(l1 or l2) same (l6 or l7)	25
☐	L12	L11 not l9	25
		DB=DWPI,JPAB,EPAB,USOC,USPT,PGPB; PLUR=YES; OP=OR	
☐	L13	("H.SUB.2")!	269900
☐	L14	("H.SUB.2")!	269900
☐	L15	("H.SUB.2")!	269900
☐	L16	("H.SUB.B")!	3604
☐	L17	("H.SUB.B")!	3604
☐	L18	("H.SUB.B")!	3604
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=OR	
☐	L19	(L13 OR L14 OR L15 OR L16 OR L17 OR L18)	272582
☐	L20	L19 and (l6 or l7)	1773
☐	L21	L20 and (botox or botulin or botulinum or botulism or bont or bonta or bontoxilysin or bota or dysport or myobloc)	263
☐	L22	L21 not l12	263
☐	L23	l19 same (botox or botulin or botulinum or botulism or bont or bonta or bontoxilysin or bota or dysport or myobloc)	8

END OF SEARCH HISTORY

DOCUMENT-IDENTIFIER: US 20040142455 A1
TITLE: Recombinant botulinum toxins having a soluble C-terminal portion of a heavy chain, an N-terminal portion of a heavy chain and a light chain

Assignee Organization Name:
Allergan Sales, Inc., Allergan Botox Limited

Detail Description Paragraph:
[0152] The botulinal neurotoxin is synthesized as a single polypeptide chain which is processed into a heavy (H; .about.100 kD) and a light (L; .about.50 kD) chain by cleavage with proteolytic enzymes; these two chains are held together via disulfide bonds in the active toxin (referred to as derivative toxin) [B. R. DasGupta and H. Sugiyama, Biochem. Biophys. Res. Commun. 48:108 (1972); reviewed in B. R. DasGupta, J. Physiol. 84:220 (1990), H. Sugiyama, Microbiol. Rev. 44:419 (1980) and C. L. Hatheway, Clin. Microbiol. Rev. 3:66 (1990)]. The heavy chain of the active toxin is cleaved by trypsin to produce two fragments termed H.sub.C (also referred to as H.sub.1 or C) and H.sub.N (also referred to as H.sub.2 or B). The H.sub.C fragment (.about.46 kD) comprises the carboxy end of the H chain. The H.sub.N fragment (.about.49 kD) comprises the animo end and remains attached to the L chain (H.sub.NL). Neither H.sub.C or H.sub.NL is toxic. H.sub.C competes with whole derivative toxin for binding to synaptosomes and therefore H.sub.C is said to contain the receptor binding site. The H.sub.C and H.sub.N fragments of botulinal toxin are analogous to the fragments C and B of tetanus toxin which are produced by papain cleavage. The C fragment of tetanus toxin has been shown to be responsible for the binding of tetanus toxin to purified gangliosides and neuronal cells [Halpern and Loftus, J. Biol. Chem. 288:11188 (1993)].

Detail Description Paragraph:
[0327] This Example involved (a) epitope mapping of the toxin A protein to determine the titre of specific antibodies directed against individual subregions of the toxin A protein when native toxin A protein is used as an immunogen, (b) affinity purification of IgY reactive against recombinant proteins spanning the toxin A gene, (c) toxin A neutralization assays with affinity purified IgY reactive to recombinant toxin A protein to identify subregions of the toxin A protein that induce the production of neutralizing antibodies, and determination of whether complete neutralization of toxin A can be elicited with a mixture of antibodies reactive to recombinant toxin A protein.

Detail Description Paragraph:
[0328] a) Epitope Mapping of the Toxin A Gene

Detail Description Paragraph:
[0329] The affinity purification of recombinant toxin A protein specific to defined intervals of the toxin A protein allows epitope mapping of antibody pools directed against native toxin A. This has not previously been possible, since previous expression of toxin A recombinants has been assessed only by Western blot analysis, without knowledge of the expression levels of the protein [e.g., von Eichel-Streiber et al, J. Gen. Microbiol., 135:55-64 (1989)]. Thus, high or low reactivity of recombinant toxin A protein on Western blots may reflect protein expression level differences, not immunoreactivity differences. Given that the purified recombinant protein generated in Example 11 have been quantitated, the issue of relative immunoreactivity of individual regions of the toxin A protein was precisely addressed.

Detail Description Paragraph:
[0343] Similar results were seen in a second experiment, in which affinity purified antibodies, directed against a single region, were added to interval 6 specific antibodies, and the effects on toxin

neutralization assessed. Only interval 4 specific antibodies significantly enhanced neutralization when added to interval 6 specific antibodies (FIG. 13). These results demonstrate that antibodies directed against interval 4 (corresponding to clone pPA1100-1450 in FIG. 9) are important for neutralization of cytotoxicity in this assay. Epitope mapping has shown that only low levels of antibodies reactive to this region are generated when native toxin A is used as an immunogen [Example 12(a)]. It is hypothesized that immunization with recombinant protein specific to this interval will elicit higher titers of neutralizing antibodies. In summary, this analysis has identified two critical regions of the toxin A protein against which neutralizing antibodies are produced, as assayed by the CHO neutralization assay.

US 20040142455A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0142455 A1**

Williams (43) **Pub. Date: Jul. 22, 2004**

(54) **RECOMBINANT BOTULINUM TOXINS HAVING A SOLUBLE C-TERMINAL PORTION OF A HEAVY CHAIN, AN N-TERMINAL PORTION OF A HEAVY CHAIN AND A LIGHT CHAIN**

(75) Inventor: **James A. Williams**, Madison, WI (US)

Correspondence Address:
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4 VENTURE, SUITE 300
IRVINE, CA 92618 (US)

(73) Assignee: **Allergan Sales, Inc., Allergan Botox Limited**, Irvine, CA

(21) Appl. No.: **10/729,039**

(22) Filed: **Dec. 5, 2003**

Related U.S. Application Data

(60) Division of application No. 10/271,012, filed on Oct. 15, 2002, which is a continuation of application No. 08/704,159, filed on Aug. 28, 1996, which is a continuation-in-part of application No. 08/405,496, filed on Mar. 16, 1995, now Pat. No. 5,919,665.

Publication Classification

(51) **Int. Cl.**[7] **C12P 21/02**; C12N 1/21; C12N 1/18; C12N 5/06

(52) **U.S. Cl.** **435/252.33**; 435/254.2; 435/69.3; 435/320.1; 530/350; 536/23.7; 435/348

(57) **ABSTRACT**

The present invention includes recombinant proteins derived from *Clostridium botulinum* toxins. In particular, soluble recombinant *Clostridium botulinum* type A, type B and type E toxin proteins are provided. Methods which allow for the isolation of recombinant proteins free of significant endotoxin contamination are provided. The soluble, endotoxin-free recombinant proteins are used as immunogens for the production of vaccines and antitoxins. These vaccines and antitoxins are useful in the treatment of humans and other animals at risk of intoxication with clostridial toxin.

12823126 PMID: 10945449

Recombinant antibodies: a new reagent for biological agent detection.

Emanuel P A; Dang J; Gebhardt J S; Aldrich J; Garber E A; Kulaga H; Stopa P; Valdes J J; Dion-Schultz A

Research and Technology Directorate, U.S. Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD 21010, USA. peter.emanuel@sbccom.apgea.army.mil

Biosensors & bioelectronics (ENGLAND) Jan 2000, 14 (10-11) p751-9, ISSN 0956-5663--Print Journal Code: 9001289

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Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Antibodies are critical reagents used in several biodetection platforms for the identification of biological agents. Recent advances in phage display technology allow isolation of high affinity recombinant antibody fragments (Fabs) that may bind unique %epitopes% of biological threat agents. The versatility of the selection process lends itself to efficient screening methodologies and can increase the number of antigen binding clones that can be isolated. Pilot scale biomanufacturing can then be used for the economical production of these immunoglobulin reagents in bacterial fermentation systems, and expression vectors with hexahistidine tags can be used to simplify downstream purification. One such Fab reagent directed against %botulinum% neurotoxin A/B has been shown to be sensitive in a variety of assay formats including surface plasmon resonance (SPR), flow cytometry, enzyme linked immunosorbent assay (ELISA), and hand-held immunochromatographic assay. Recombinant antibodies can provide another source of high quality detection reagents in our arsenal to identify or detect pathogens in environmental samples.

Descriptors: *Biosensing Techniques; *Immunoglobulin Fab Fragments --immunology--IM; *Recombinant Proteins--immunology--IM; Animals; Antibody Affinity; Antibody Specificity; Botulinum Toxins--immunology--IM; Enzyme-Linked Immunosorbent Assay; Mice; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.

CAS Registry No.: 0 (Botulinum Toxins); 0 (Immunoglobulin Fab Fragments); 0 (Recombinant Proteins)

Record Date Created: 20001201

Record Date Completed: 20001201

Source notes